REMARKS

Reconsideration of this patent application is respectfully requested in view of the foregoing amendments, and the following remarks.

The amendments to this patent application are the following. Claim 11 has been amended as follows:

"A therapeutic method for the treatment of ophthalmic diseases of the posterior segment of the eye selected from the group consisting of bacterial or fungal endophthalmitis, viral retinitis, vitreoretinopathy, toxoplasmosis, uveitis, tumours, vascular diseases, diabetic retinopathy, age-related macular degeneration, and glaucoma, said method comprising the intravenous or topical ocular administration of a therapeutically effective amount of ~~solid lipidic nanoparticles (SLN) comprising~~ a pharmacologically active substance suitable for the treatment of said ophthalmic diseases, said active substance being incorporated into solid lipidic nanoparticles (SLN) ~~wherein said SLNs are prepared~~ by:

a) admixing a molten lipid substance containing a drug or its complex with a mixture comprising water, a surfactant, a cosurfactant and optionally a counterion of the drug, pre-warmed

to a temperature at least equal to the melting temperature of said lipid substance, thus obtaining a microemulsion having a temperature at least equal to the melting temperature of said lipid substance;

b) dispersing the microemulsion obtained in step a) in water or in an aqueous medium cooled to a temperature comprised between 2 and 5.degree.C., thus obtaining a dispersion of solid lipidic nanoparticles incorporating the drug;

c) washing the dispersion obtained in step b) with water or with an aqueous medium by diafiltration with the almost total elimination of the surfactant and the cosurfactant;

d) drying the dispersion obtained in step C) by lyophilisation or by spray drying or by evaporation, thus obtaining the solid lipid nanoparticles (SLNs) with the drug incorporated."

The list of ophthalmic diseases of the posterior segment of the eye finds support on page 1 in lines 15 to 21 of the present Specification.

REJECTIONS UNDER 35 USC §112

The ophthalmic diseases of the posterior segment of the eye have been limited to those listed in the specification of the

current application in order to meet the enablement requirements, as requested by the Patent Examiner in the outstanding Office Action.

As far as the indefiniteness of the previously presented Claim 11 is concerned, the Patent Examiner asserts that it is not clear which subject matter the Applicants regard as the invention.

Indeed, the previously presented Claim 11, as well as the currently amended Claim 11, refers to a therapeutic method of treating ophthalmic diseases of the posterior segment of the eye, wherein the used solid lipid nanoparticles have been defined as product-by-process.

As a matter of fact, only the solid lipid nanoparticles obtained according to said process have been proved to have the chemical-physical properties suitable for being used in the claimed method, i.e. successfully and efficiently achieving and treating the posterior part of the eye where the active substance incorporated therein can be delivered.

For all the reasons set forth above, the present

Specification and all the claims, are firmly believed to be in complete compliance with all the requirements of 35 U.S.C. 112, both first paragraph and second paragraph. Withdrawal of this ground of rejection is respectfully requested.

REJECTIONS UNDER 35 USC § 102

In the outstanding Office Action, with reference to *Cavalli et al.* the Patent Examiner affirms that:

SLN of *Cavalli* would inherently reach the posterior segment as the results are the same when the mode of administration and the components of the composition utilized for the method of treatment are met. It is noted that *Cavalli* also teaches its use for bacterial endophthalmitis which is a condition in the posterior segment of the eye.

In other words, the Patent Examiner is persuaded that each part of the eye can be equally and automatically reached. For example, merely treating the cornea is possible allegedly, even though it requires definitely disregarding the complexity of the eye anatomy. The Applicants absolutely disagree with the above

simplistic deduction. As a matter of fact, none of the cited prior art documents address or even only mention the posterior part of the eye. Thus accordingly there is no suggestion of a method of treating the posterior part of the eye.

Indeed, the great difficulties in reaching the posterior segment of the eye, like the retina, are clearly addressed in the introductory section of the present patent application (Page 1, lines 4 to 6), where it is well explained that "the therapeutic treatment of the eye has been essentially directed towards the administration of drugs directly to the tissues and the fluids of the anterior segment of the eye", as *Cavalli et al.* "The eye is an isolated and highly protected organ. In particular, the tight junctional complexes of the retinal pigmented epithelium and the retinal capillaries constitute the blood-retinal barrier for which the systemic administration of drugs does not succeed in reaching an adequate level within the posterior segment of the eye. On the other hand, even with topical administration, only small amounts of drug reach the retina, as penetration through the external walls of the eye is very low."

The historical difficulty in reaching the posterior segment of the eye, i.e. the reasons why many of the diseases affecting

the same were unsatisfactory treated at the time the invention was made, is confirmed by the fact that the Patent Examiner has found no prior art documents at all regarding the treatment of the posterior segment of the eye.

With reference to the cited prior art documents, *Cavalli et al.* fails to disclose any of the following essential feature of Claim 11:

- the therapeutically effective treatment of the posterior part of the eye,
- the identification of the ophthalmic diseases specifically affecting the posterior part of the eye,
- the limitation to pharmacologically active substances suitable for the treatment of said ophthalmic diseases, said active substance being incorporated into solid lipidic nanoparticles.

The Patent Examiner asserts that bacterial endophthalmitis is a disease already mentioned in *Cavalli et al.* The Applicants wish to point out that even if bacterial endophthalmitis can affect the eye at different levels of severity as well as at different points of the eye, however, Claim 11 is expressly

limited to the case where said disease affects the posterior part of the eye. Thus *Cavalli et at.* definitely teaches away from the claimed method for the purposes of the present invention.

In view of the above, the currently amended Claim 11 is therefore new and novel over *Cavalli et al.*, thus the claim rejection under 35 USC § 102(a) should be withdrawn accordingly.

As far as *Amselem et al.* are concerned, it should be noted this this other reference additionally fails to disclose:

- the therapeutically effective treatment of the posterior part of the eye,
- the identification of the ophthalmic diseases specifically affecting the posterior part of the eye,
- the limitation to pharmacologically active substances suitable for the treatment of said ophthalmic diseases, said active substance being incorporated into solid lipidic nanoparticles, and

- the solid lipid nanoparticles expressly defined as product-by-process and thus so limited.

The Patent Examiner asserts that "Amselem teaches particles with a solid lipid core with a particle size distribution in the range of 10-250 nm which is a nanoparticle with the inclusion of several drugs including beta-adrenergic blockers (e.g. adaprolol and timolol) for glaucoma, cannibinoids, antifungal, antibiotics, and corticosteroids for treatment of eye conditions." (page 17 of the Office Action).

However, as already argued in the previous response, *Amselem et al.* indeed relate to nano-emulsions achieving at most the technical effect of lowering the Intra-Ocular Pressure (IOP), which is only one of the risk factors for glaucoma, considering that it is known that in some populations only 50% of patients with primary open angle glaucoma actually have elevated ocular pressure. In fact, glaucoma is a disease of the optic nerve, wherein the nerve cells in the front of the optic nerve (the ganglion cells) die.

Reduction of IOP is usually achieved by topically treating the anterior segment of the eye (i.e. the cornea and the aqueous fluid which is in the anterior chamber of the eye), while an effective treatment of glaucoma requires the drug to reach the optic nerve in the posterior segment of the eye (close to the

retina).

Consequently, *Amselem et al.* actually teach at most how to prevent one of the main glaucoma risk factors, but do not teach how to effectively treat glaucoma, being a disease of the posterior segment of the eye, once it has occurred.

In view of the above, the currently amended Claim 11 is therefore new and novel over *Amselem et al.* Hence the claim rejection under 35 USC § 102(b) should be withdrawn accordingly.

REJECTIONS UNDER 35 USC ~ 103

The currently amended Claim 11 is also non-obvious over the abovementioned prior art documents.

As a matter of fact, the skilled person would have never considered the publication of *Cavalli et al.* since it clearly does not pertain to the field of endeavor of the present invention. Indeed, as above explained, *Cavalli et al.* are directed to the treatment of the anterior part of the eye, which is the part anatomically exposed, thus directly accessible, while definitely disregarding the posterior part of the eye, which is

the part anatomically deepest placed and highest protected by many tissues, as discussed above.

Amselem et al., as above argued, indeed do not treat a disease, but at most prevent the worsening of a risk factor. Therefore, also this document does not teach the skilled person to solve the above reported difficulties in reaching and treating the posterior segment of the eye.

In this regard, it should be noted that the same applies also with reference to *Schwartz*, similarly only treating the reduction of the IOP (see claim 11).

In order to further support the patentability of the claimed invention, a Declaration of Prof. M.R. Gasco has been herewith provided, being one of the inventors. The publications of two studies have been annexed to said Declaration, wherein the efficacy of the claimed method has been demonstrated.

Particularly, these studies are as follows:

1) Program#Poster#:4464/D630

Gargini M. C. et al., "Inhibition of Ceramide de novo Synthesis in an Animal Model of Retinitis Pigmentosa: II. Effects on Photoreceptor Survival and Function", ARVO 2009 annual meeting. pp 50, D629--, Fort Lauderdale, 2009;

2) Program#Poster#:4463/D629

Ghidoni R. et al., "Inhibition of Ceramide do novo Biosynthesis in an Animal Model of Retinitis Pigmentosa: I. Morphological and Biochemical Effects", ARVO 2009 annual meeting, D630--. Fort Lauderdale, 2009.

Said studies demonstrated in a mammalian model of Retinitis Pigmentosa (RP) that it is possible to decrease the rate of apoptotic death of photoreceptors by lowering retinal ceramide levels through inhibition of the de novo biosynthesis of this molecule. Non invasive, chronic administrations of solid lipid nanoparticles according to the present invention loaded with SPT inhibitors are effective in increasing the survival rate and functional responses of photoreceptors. Since typical RP has a naturally slow evolution, a further delay in the degeneration of

photoreceptors might be considered itself therapeutic. Particularly, it is known that a small increase in the survival of rods produces a proportionally larger increase in the survival rate of cones, the only cells upon which residual vision is based in RP patients.

Therefore, while said studies further confirmed the efficacy of the claimed method, at the same time, these results are even more surprising when considering that, as above noticed, no prior art at all has been found by the Examiner addressing the treatment of the posterior segment of the eye, thus preventing the skilled person from even considering this possibility. Additionally, the Applicants wish to remark that the only alternative way to reach the retina was intravitreal injections that are extremely painful and extremely tricky in terms of risks of injuring the eye and promoting infections. Therefore, since these injections are definitely undesirable and unsatisfactory under many points of view, the contribution of the claimed invention over the prior art is even more evident and appreciable.

This further means that at the time the invention was made, the skilled person actually had no pertinent background prior art

from where to start to solve the problems solved by the claimed invention.

In this regard, Applicants are of the opinion that the Patent Examiner deducted the obviousness of the claimed method on a basis of a hindsight reconstruction of the prior art to produce the present invention by having knowledge of the same, i.e. on the basis of an ex-post facto analysis which is not permissible.

As a matter of fact, there is no teaching for a method of treating specific ophthalmic diseases of the posterior segment of the eye through intravenous or topical ocular administration of a therapeutically effective amount of a pharmacologically active substance suitable for the treatment of said ophthalmic diseases, said active substance being incorporated into solid lipidic nanoparticles obtained by a specific process.

PROVISIONAL DOUBLE PATENTING OBJECTION

In view of this reiterated objection, the Applicants reserve the right to cancel Claims 89 and 91 of the copending US application No. 11/629141, once the US patent has been granted for the current US application.

CONCLUSIONS

In view of the above, Applicants submit that the present patent Application as currently pending is in condition for allowance on the grounds that the amendments provided fully overcome the objections and rejections raised in the outstanding Office Action.

Withdrawal of the prior art rejections under 35 U.S.C. 102 and 35 U.S.C. 103 is respectfully requested.

A prompt notification of allowability is respectfully requested.

Respectfully submitted,
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Enclosure: 1. Petition for 3 Month Extension of Time-Small Entity
2. RCE Transmittal
3. Declaration of Dr. M.R. Gasco
4. Two Reference Articles

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Amy Klein